

Inhaled CO₂ to Reduce Lung Ischemia and Reperfusion Injuries: Moving Towards Clinical Translation?

Claire H. Masterson, PhD^{1,2}

Daniel O'Toole, PhD^{1,2}

John G. Laffey, MD, MA, BSc, FCAI^{1,2,3}

RECEIVED FROM:

¹Anaesthesia, School of Medicine, National University of Ireland, Galway, Ireland.

²Regenerative Medicine Institute (REMEDI) at CÚRAM Centre for Research in Medical Devices, Biomedical Sciences Building, National University of Ireland Galway, Galway, Ireland.

³Department of Anaesthesia and Intensive Care Medicine, Galway University Hospitals, Galway, Ireland.

CORRESPONDENCE: John G. Laffey, Anaesthesia, School of Medicine, Clinical Sciences Institute, National University of Ireland, Galway, Ireland

Tel: (353) 91- 495662

email: john.laffey@nuigalway.ie

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Partial occlusion of the pulmonary artery (PA) may contribute to the lung injury seen following complex surgical procedures such as lung transplantation, cardiopulmonary bypass, and pulmonary arterial thrombectomy or embolectomy, and even closure of patent ductus arteriosus in infants. Similar injury may also occur in the context of resuscitation following cardiac arrest or from shock states resulting in hypoperfusion and cellular dysoxia. Pre-clinical models have given some insight to the outcomes of PA occlusion in spontaneously breathing (1, 2) and ventilated animal models (3). Nevertheless, the precise mechanisms by which pulmonary arterial ligation causes lung injury remain poorly understood. This is further complicated by the fact that restoring pulmonary arterial perfusion, which is pivotal to restoring tissue viability, leads to a reperfusion injury, with oxidative stress and activation of inflammation further contributing to tissue injury (4, 5).

Understanding mechanisms by which PA ligation directly induces lung injury is central to developing mitigation strategies and potential therapies. Here, Marongiu and colleagues report the development of a model of prolonged (48 hour) unilateral (left) lung pulmonary artery ligation in a mechanically ventilated large animal (porcine) model (6). Left pulmonary artery ligation led to progressive collapse and underventilation of the ipsilateral lung and to lung edema and overstretch of the 'normal' lung, leading to maldistribution of ventilation, and resulting in a ventilation induced lung injury (VILI) of the perfused lung, with lung edema and decreased compliance, and frank histological injury. Lung infiltration with leukocytes of the innate and adaptive immune systems was demonstrated.

Marongiu and colleagues also demonstrate the potential for 'therapeutic hypercapnia' (7), induced by delivering inspired 5% CO₂, in attenuating PA ligation induced lung injury. This work extends previous studies whereby 5-6% environmental CO₂ reduced lung injury in spontaneously breathing animals following PA ligation (8). Marongiu and colleagues data provide new insights into the mechanisms by which inspired CO₂ may exert these protective effects. Inspired CO₂ preserved the function of both the left (PA ligated) and right lungs and reduced the inflammatory response to PA ligation. Severe airway hypocapnia, which is a consequence of PA occlusion, may be directly deleterious. Hypocapnic alkalosis has been demonstrated to directly injure the lung, increasing capillary permeability and worsening ischemia-reperfusion (IR) induced lung injury (9). Hypocapnia also alters surfactant composition and impairs function (10), which may explain the decrease in compliance in the ipsilateral lung. These effects are reversed by 5% inspired CO₂ (10). Avoidance of airway hypocapnia may therefore be an important contributor of the protective effect demonstrated.

The effects of inspired CO₂ on reducing contralateral (right) lung injury may be due to the potential for hypercapnic acidosis to attenuate the lung inflammation and injury caused by excessive mechanical stretch (11). Inspired CO₂ therapy suppresses ventilation induced lung inflammation and via a mechanism involving inhibition of NF-κB activation (12, 13). Wu and colleagues found that inspired CO₂ lung IR induced injury via inhibition of the NF-κB pathway(14), while NF-κB inhibition also underlies the protective effect of hypercapnic acidosis in reducing hepatic IR injury (11), suggesting this may be key underlying mechanism of action following PA occlusion.

These findings also add to existing evidence suggesting that inhaled CO₂ may have therapeutic potential in the setting of lung ischemia-reperfusion induced injury. Shibata and colleagues first demonstrated that inspired CO₂ attenuated IR induced injury in the isolated rat lung (15). Subsequent reports demonstrated that inspired CO₂ reduced lung injury following *in vivo* pulmonary and systemic IR injury (16). Inspired CO₂ decreased lung injury even when initiated after the commencement of reperfusion, highlighting its clinical promise (17). Importantly, the beneficial effects of inspired CO₂ appeared to be a function of the systemic acidosis generated rather than the hypercapnia *per se*. In fact, induced metabolic acidosis also reduced IR injury, while buffering a metabolic or hypercapnic acidosis abolished the benefit (9).

The study has a number of limitations worth considering. Firstly, CO₂ was applied early, at the time of pulmonary artery ligation. While this may be relevant to situations where pulmonary artery ligation is predictable, the effects of CO₂ administration at later timepoints would be worth exploring. Second, it is unclear whether the effects were due, at least in part, to the systemic effects of hypercapnic acidosis induced by the 5% CO₂. An interesting experiment to dissect these contributions would be to apply the inspired CO₂ only to the ligated lung, as this would determine the extent to which avoidance of alveolar hypocapnia contributes to the effects seen, while avoiding a systemic hypercapnic acidosis. Third, animals from the inspired CO₂ group were not randomized with those from other groups for technical reasons. Lastly, the rationale for the variability in group size between the control and treatment groups is unclear. While the authors acknowledge the discrepancies and point to the variability of the development of injury, this effect should also be true for the treatment group.

What is the relevance of the findings of Marongiu *et al.* to the critical care practitioner?

Ischemia/reperfusion injury is a critical consideration in a wide range of lung injuries as well as a risk factor in many surgical procedures (18). Although the issue of reperfusion injury is not considered, it compartmentalizes the injury parameters that are incurred due to ischemia and the resultant promise of using inhaled CO₂ as a therapeutic. This study demonstrates a clear benefit of inspired CO₂ in a ligated pulmonary artery model, although the intervention is at an early timepoint. It adds to a growing body of work accumulated to this point demonstrating the therapeutic potential of inspired CO₂ for IR injuries. This possible therapeutic option is relatively simple to implement and test, has few obvious side-effects and critical care physicians are very familiar with managing hypercapnia in the critically ill patients.

In conclusion, we welcome this addition to the evolving body of evidence regarding the beneficial effects of CO₂ in acute ischemia induced lung injuries. We look forward to following the further studies in this area in more advanced preclinical models and perhaps ultimately in clinical studies.

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